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REC'D 25 AUG 2004

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ISPT-1000	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/18003	International filing date *(day/month/year)* 09 June 2003 (09.06.2003)	Priority date *(day/month/year)* 10 June 2002 (10.06.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 48/00; C07H 21/00; C12Q 1/68 and US Cl.: 514/44; 435/6, 325, 375; 536/23.1, 24.5		
Applicant ISIS PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09 January 2004 (09.01.2004)	08 August 2004 (08.08.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 872-9306	Authorized officer J. D. Schultz, Ph.D. F. Roberts for Telephone No. 571-272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International app[redacted] No.
PCT/US03/18003

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-111 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 112 and 113, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages None, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-35, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 5-9, 15-20	YES
	Claims 1-4, 10-14	NO
Inventive Step (IS)	Claims 15-20	YES
	Claims 1-14	NO
Industrial Applicability (IA)	Claims 1-21	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 15-20 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest methods of treatment using IRAK-1 targeted antisense compounds in methods of treating disease.

Claims 1-20 meet the criteria set out in PCT Article 33(4), and thus possess industrial applicability because the subject matter claimed can be made or used in industry.

Please See Continuation Sheet.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claims 1-4, and 10-14 lack novelty under PCT Article 33(2) as being anticipated by Guo *et al.*
The invention of the above claims is drawn to modified antisense compounds 8 to 80 nucleobases long that hybridize with and inhibit IL-1 Receptor Associated Kinase-1 (IRAK-1), and methods of using same.

Guo *et al.* teaches modified antisense compounds 8 to 80 nucleobases long that hybridize with and inhibit IL-1 Receptor Associated Kinase-1 (IRAK-1), and methods of using same. See Materials and Methods of Guo.

Claims 1-14 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Baracchini *et al.* and Taylor *et al.*

The invention of the above claims is drawn to antisense compounds that target IRAK-1 or said compounds comprising internucleoside, nucleobase, and 2' modifications, chimeras, or compositions comprising said compounds and pharmaceutically acceptable diluents thereof.

Guo et al teach the cDNA sequence encoding IRAK-1. Guo does not teach antisense sequences comprising nucleobase, and 2' modifications, and chimeras.

Taylor et al. teach that antisense oligonucleotides 7-30 nucleotides long can be synthesized to inhibit the expression of any protein provided the cDNA sequence is known. Taylor *et al.* also indicate that making and using such oligos are available to those of ordinary skill in the art, that it is common practice to chemically modify the such oligonucleotides to prolong their bioactivity, and also teach that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Baracchini *et al.* teach that antisense oligonucleotides can be used for research purposes, and also teach that preferred antisense oligonucleotides are modified in their sugar, backbone linkage and nucleobase composition (col. 6). Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al provide specific embodiments of such modifications at columns 6-8 and in Example 1. These specific examples taught by Baracchini et al include the presently claimed phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric oligonucleotides. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture. Table 1 exemplifies the successful practice of general antisense design taught at columns 8-10. Column 4 teaches various carriers for antisense delivery. Baracchini *et al.* also teaches at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length. Baracchini is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

It would have been obvious to one of ordinary skill in the art to modify the antisense sequence of Guo to as taught by Taylor and Baracchini IRAK-1 expression for inhibition of IRAK-1 expression, and further, it would have been obvious to one of ordinary skill in the art to incorporate modifications as taught by Baracchini *et al.* a into said antisense compounds.

One would have been motivated to create such compounds because Guo et al. expressly teach antisense compounds that

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

target and hybridize to IRAK-1. One would have been motivated to modify said antisense compounds as taught by Baracchini *et al.* a because they teach that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation.

Finally, one would have a reasonable expectation of success given that Taylor teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%, and since Baracchini *et al.* and Bennett *et al.* both teach making modified antisense compounds targeted to distinct regions of a target gene, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

----------NEW CITATIONS----------

US 5,801,154 A (BARACCHINI et al.) 01 September 1998 (01.09.1998), entire document.

TAYLOR et al. Antisense oligonucleotides: a systematic high-throughput approach to target validation and gene function determination. Drug Disc. Today, 1999, Vol. 4, No. 12, pages 562-567, entire document.